Review Article

Induced Pluripotent Stem Cell Meets Severe Combined Immunodeficiency

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Abstract

Severe combined immunodeficiency (SCID) is classified as a primary immunodeficiency, which is characterized by impaired T-lymphocytes differentiation. *IL2RG, IL7Ralpha, JAK3, ADA, RAG1/RAG2,* and *DCLE1C* (Artemis) are the most defective genes in SCID. The most recent SCID therapies are based on gene therapy (GT) of hematopoietic stem cells (HSC), which are faced with many challenges. The new studies in the field of stem cells have made great progress in overcoming the challenges ahead. In 2006, Yamanaka et al. achieved "reprogramming" technology by introducing four transcription factors known as Yamanaka factors, which generate induced pluripotent stem cells (iPSC) from somatic cells. It is possible to apply iPSC-derived HSC for transplantation in patients with abnormality or loss of function in specific cells or damaged tissue, such as T-cells and NK-cells in the context of SCID. The iPSC-based HSC transplantation in SCID and other hereditary disorders needs gene correction before transplantation. Furthermore, iPSC technology has been introduced as a promising tool in cellular-molecular disease modeling and drug discovery. In this article, we review iPSC-based GT and modeling for SCID disease and novel approaches of iPSC application in SCID.

Keywords: Hematopoietic Stem Cell Transplantation, Induced Pluripotent Stem Cell, Primary Immunodeficiency, Severe Combined Immunodeficiency

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Introduction

Severe combined immunodeficiency (SCID) is classified as a primary immunodeficiency (PID), which is characterized by impaired T-lymphocyte differentiation. SCID is a monogenic, heterogeneous, and life-threatening syndrome (1). Considering that both humoral and cellular adaptive immunity are involved, this immunodeficiency is called "combined" because in T^-B^- phenotypes of SCID, T-cell development, as well as B-cell development is affected. In T^-B^+ phenotypes, the absence of normal T-helpers leads to defective antibody production by normal B-cells. In some subtypes of SCID, the disease can also be accompanied by defective natural killer (NK) cells. These different phenotypes are due to mutations in several genes, which lead to appear in different stages of T-cell development (Fig.1). The worldwide prevalence of SCID is estimated to be in 50,000 to 100,000 of the young population and constitutes 7% of PID patients. Approximately 90% of genetic defects in different forms of SCID have been identified (2, 3). The latest therapies regarding SCID are based on gene therapies (Table 1), which so far are faced with many difficulties (4-18). The new studies in the field of stem cells have made considerable progress in overcoming the challenges ahead.

A review on induced pluripotent stem cell

In 2006, Takahashi et al. (19) achieved "Reprogramming" technology by introducing OCT4, KLF4, SOX2, and C-MYC reprogramming factors (RFs), which are responsible for embryonic-like state, into human fibroblasts. These RFs, known as OKSM factors, generate induced pluripotent stem cells (iPSC) from a somatic cell and reverse its state back into embryonic status, which can later differentiate to various human cells. IPSC-derived pre-differentiated or differentiated cells can be used for transplantation in patients with abnormal or poorly functional specific cell lineage. Considering that harvested cells are autologous, there is no risk of immunological rejection (fully matched HLA-profile) and no concern regarding the low number of transplantable cells. Furthermore, preparing these pluripotent stem cells is a non-invasive method (20).

In addition to other aspects of iPSC-based therapies, there are various studies in the field of cancer and immunodeficiency that led to the creation of iPSC-derived cytotoxic T-lymphocytes (iCTL) and iNKT-Cells, which have major roles in the immune system. The medical applications of iPSC are not limited to cell therapy. Recently, iPSC technology has been introduced as a promising tool for *in vitro* cellular-molecular disease modeling, drug discovery, and *ex-vivo* regenerative medicine, including organogenesis and GT (21, 22).